Dan's in that --

MS. THORNTON: Could you identify yourself?

DR. BRINT: Dr. Stephen Brint.

In this slightly younger group, in the 38- to 39-year-old group, it's a little bit younger than we see in our typical LASIK population of the over-40ish group, one thing, and then, two, relative to glare and halos, obviously this is a symptom that this technology is attempting to address, and as far as trying to screen out people already complaining of this, there was none. As far as trying to screen out patients with preoperative history of dry eye, in particular, there was none.

Also, I think that certainly now in contemporary LASIK surgery, we're much more aware of the dry eye potential than we were as far as some of the patients that Ron was referring to that are now appearing in his database and that these patients were perhaps treated more aggressively as we treat all patients more aggressively now for dry eyes, punctal occlusion and other things much more aggressively routinely in our every-day LASIK practices than we did several years ago.

DR. WEISS: I would just add one thing. On Table 34, if we include the patients in the spherical cohort who are saying that their symptoms are not only significantly worse but just plain worse, you actually have

about 32 percent saying the dryness was worse or significantly worse. So it's still not trivial, and I think if we are looking at the worse category, it significantly increases the number of complaints.

Did you have a follow-up question?

DR. BRADLEY: I did. On a related issue that was raised a few minutes ago -- that is, the rather high dissatisfaction rates amongst your patients -- I think Dr. Pettit indicated that this was probably due to the residual myopia present in these patients.

It seems to me it would be worth establishing that as a fact or not. I think some correlation analysis might allow you to do that and maybe including something like that in the labeling because if indeed the dissatisfaction is due to undercorrection, clearly that can be at least remedied by wearing a spectacle or contact lens overcorrection, whereas if dissatisfaction was due to some other uncorrectable problem, that's a more serious dilemma and I think perhaps labeling should perhaps clear that up.

DR. PETTIT: Yes. This is George Pettit again.

We have done some analysis. It is correlated, and we can pull that, if you want, but there is definitely a link. It doesn't explain everybody that's unsatisfied, but there's definitely a correlation there.

DR. HAKIM: Omar Hakim.

I just operated on a good friend of mine who's an optometrist, and when he wanted to get his eyes done, he was about a -4, wanted to have his eyes done about almost 10 months ago now, and was talking about having conventional because he had seen the results that we had gotten with conventional, the LADARVision, and I showed him some of the early results that we had been presenting at some of the meetings on Custom. He decided to have Custom, ended up, of course, mildly undercorrected in one eye, about -75, and I just did a conventional retreatment on him, I think it was last Friday or just this Friday past, and he noted an immediate improvement in quality of his vision in that eye. So you know, please do remember these patients have been enhanced. These are all primary treatments, and I think with enhancements, you know, certainly we can probably bring these people up and from what George is saying, there is a correlation.

DR. WEISS: I would actually go back to the sponsor's own slides, on page 22, that you indicate for better or significantly better, the mean MRSE was -.26 to -.36, worse to significantly worse was -.46 to -.70. So I don't know. I assume that's the data that you're referring to that you've shown us.

We're going to go on to questions by Mr. McCarley, Dr. Swanson, Dr. Owsley, and Dr. Maguire.

MR. McCARLEY: This is Rick McCarley.

I just had, I guess, a comment on Dr. Grimmett's statement about the comparison of the PERK dissatisfaction rates to this study's dissatisfaction rates. The Ns are significantly different, as I understand it. We have 139 patients in this and the PERK study was much larger. So an error is certainly built in and not being considered, but perhaps there are others in the room that have actually conducted patient surveys or questionnaires, and I trust them on very large numbers, but anything less than 10,000, I think you have, you know, problems built in, like did they get a parking place close to the door?

I guess I would caution the panel as to whether we should be making labeling changes to placate certain small segments of the population believing that that's going to change necessarily how a surgeon would pick the patient after they've already been educated on which patients should be included. In other words, if a surgeon performs surgery on a patient they should not have, the outcome's going to be the same whether or not they told the patient. The question is will the patient make a different decision? I've spoken with patients myself who probably would have gone ahead with the decision because they didn't understand the total consequences. So I guess it's just a

comment. I'm not sure we can label ourselves out of this. Certainly more education and more experience with this will give us a better idea of where it goes.

DR. WEISS: Dr. Swanson?

DR. SWANSON: Bill Swanson.

You've been very forthcoming. It's a lot of data analyses. One of the things that you did that was useful was to look at the clinically significant change, and then there's mentioned like in the summary that contrast sensitivity more had a clinically significant improvement than loss. However, those numbers are very small, and if you do confidence intervals for percentages, you can get some sense or some other type of statistical measure, are they actually different? It's easy to say 4 percent is twice as big as 2 percent, but then the question arises, is that data statistically any different or could it be because of the small sample size?

DR. PETTIT: We have not done a more detailed analysis than the simple P values and whatnot that you saw there. So we can do that. We don't have that data right handy.

DR. WEISS: Dr. Owsley?

DR. OWSLEY: Cynthia Owsley.

Many of your analyses were on basically change scores before and after surgery, whether it was referring

to acuity or wavefront or whatever. However, your measures that really are components of health-related quality of life, it seems that your analyses, unless I missed something, focused on postsurgery only, and your change score was by inference of asking people whether there have been significant changes and they're answering in a subjective way.

I'm wondering if you did any of your symptom lists or quality of vision instruments before surgery and whether the change data has ever been looked at.

DR. PETTIT: We're bringing Dr. Stevens again to address that.

DR. STEVENS: Christy Stevens, Alcon.

There's a preop questionnaire data in the PMA and it's rated on the scale from none to severe. Postoperatively, the patients were asked to specifically rate their change, significantly worse, significantly better. They were not asked to rate them on a scale from none to severe postoperatively.

DR. OWSLEY: So the same instruments were not used pre and post, if I understand you correctly.

DR. STEVENS: That's correct.

DR. WEISS: Dr. Maguire?

DR. MAGUIRE: Dr. Maguire.

Dr. Durrie said earlier that this is a step on

the way to improvement, and it appears, and correct me if I'm wrong, that this is probably the seventh step in your algorithm where you've approached the panel, is that correct?

DR. PETTIT: Seventh iteration of our Custom treatment algorithm.

DR. MAGUIRE: Seventh iteration, and it appears that you made a judgment to bring spherical correction before the panel but not astigmatic. What fell short in your non-spherical group that caused you to hold back? Just a second. To give you a rationale behind that, as you said earlier, marketing is 85-percent confusion and 15-percent commission, and so there's been a lot of that around in this particular technology, and as it's already been mentioned, people do have high expectations.

So the question that comes in mind as a clinician is, when has there been enough step occurred, and should the step be bigger? So I'd be interested to know what your criteria were for not stepping forward with your astigmatic group but stepping forward for your spherical group.

DR. WEISS: I would like to just direct this to Mr. Whipple because this is information that the sponsor does not want to approval for, and I would like to know whether this is appropriate for them to have to answer this

question or address this question or not.

MR. WHIPPLE: I think they can make the judgment. If they feel like answering it, they can.

DR. WEISS: Okay. It's in your court.

DR. PETTIT: No, I'm happy to answer the question.

The honest answer is that in the astigmatic cohort, we did meet all the safety parameters as Dr. Durrie indicated, and we were effective, but in an honest assessment, we were not as effective as our conventional surgery in the treatment of astigmatism. We found out the trends that explained that and we decided we can fix this. Why don't we fix this and get the best possible astigmatic outcome before we pursue astigmatic approval, and it was a judgment call just on our part.

DR. MAGUIRE: And I thank you for that honest answer, and then in follow-up on that, then as I look at the basic clinical data for your spherical cohort, what it appears is by the small numbers and the higher myopic range, that there's more scattering results and there's a very small sample and so that in, you know, the mean is kind of pushed towards emmetropia by the large number of lower corrections placed in there, and looking at the chart in the medical officer's review on page 30, it does appear that there gets to be more scatter when you get above -5,

and you've already talked about patient dissatisfaction increasing with undercorrection, and we've also discussed that the marketing issues that have led to high patient expectations.

So how did you decide that in this group above -4, that was acceptable as compared to the astigmatic group?

DR. PETTIT: Well, in general, even at the high end of the range, we have relatively good outcomes in terms of BCVA numbers. The scatter is higher at the high end and that's what we see with all of our refractive surgical procedures. So again, it was a judgment call, that in general that group did well with more scatter and some patients that were more undercorrected than they were at the lower ranges.

DR. MAGUIRE: But would you agree that a patient coming in with high expectations may be more likely to be disappointed if their spherical correction was greater than -4 preoperatively?

DR. PETTIT: I actually would invite our clinicians to comment on that as well. They have more likelihood of being undercorrected after surgery. The accuracy is less when you get to the higher end, and we would need to communicate to them to try to set their expectation realistically.

DR. MAGUIRE: So you would agree that that would be a very appropriate thing to put in the labeling and to give particular emphasis to it with this particular submission because of the claim for higher levels of superior vision. We're not just correcting emmetropia but we're promising superb optical resolution of emmetropia.

DR. HAKIM: This is Dr. Omar Hakim.

You know, I would like to add, you know, maybe sort of retracing some of the ground that I went through in some of the slides that even in that higher myopic group that you referred to, Dr. Maguire, above -5 and -6, that, you know, again 92 percent of patients between -5 and -5.99 had uncorrected visual acuity of 20/25 and above -6 still 75 percent of patients had uncorrected acuity of 20/25, and overall in that -5 and up group, fully 75 percent of patients were within plus or minus a half diopter of emmetropia. So you know, while there was more scatter, you know, I definitely agree with you, as we see even with conventional surgeries or any type of platform, you know, those are numbers that as a clinician I would consider very acceptable.

DR. MAGUIRE: I agree with you totally. I find it totally acceptable, too, but I think the labeling must reflect the higher expectation of the patient regarding this, that this isn't conventional and we're not supposed

to be as encouraging conventional ideas. We're supposed to be using ideas that are promising to the patient, that are a significant step ahead where we have to make it clear that it's just a moderate step ahead on the way to the ideal.

DR. DURRIE: This is Dan Durrie.

I think that there is a balance here, and Leo, I think you're getting at a very important thing, is that, if the indications for use and the claims that are being -- I mean, if you all decide that the claim of superior vision is something that is going to be tied to this, then those claims will be balanced out by the data that at the higher level, less people will meet those claims.

On the other hand, you have to really look at this as an elective surgery that somebody's undergoing and the patient who is a -1 has a less significant visual handicap than the patient who's a -6 triope. So if I apply this to my practice, the happiest patients that I have are the patients in the higher level, even if they have more symptoms of night glare because their disability of their myopia and the lower-order aberrations were so much greater.

So I think we've got to be a little cautious here because, you know, you say it in such a way that if we are claiming superior vision and marketing at that level,

that's one thing. I think we should be cautious on both sides of that, too. So balancing that, I wouldn't want to go out and just say that higher myopes are less satisfied with refractive surgery, Custom or not Custom. That certainly is not true, but the situation is is that it is harder to sink a long putt than a short putt, and I think we've seen that in all of the clinical trials and this is just typical of it.

DR. WEISS: Dr. Maguire, did you have any follow-up questions?

DR. MAGUIRE: That ends it.

I just wanted to say, I realize this is a dilemma, and wisdom's the ability to make a decision when you're faced with a dilemma, and reasonable people can disagree on what's wise. All I'm saying is, I'm looking at this not from a physician standpoint, I'm looking at it from a patient standpoint, taking into consideration what I've heard from the sponsor which is that the higher myopes are more dissatisfied and that there's at least a sense, maybe it's not backed up by data, that the patients that are undercorrected tend to be more dissatisfied perhaps because they have a higher level of expectation with this particular technology than they would with conventional and somehow that spirit that we all agree on has to find its way into labeling to avoid patient dissatisfaction from

For the 35- and 46-age categories, the cell density at time of implant was approximated by assuming .6 percent yearly cell loss due to normal aging, with the .6 percent figure taken from the 1997 Bourne article, as referenced earlier by Drs. Edelhauser and McCarey. This was done to provide a check of whether the minimum inclusion criteria per age group were reasonable.

The third column, the estimated rate of cell loss per year, represents potential rates of loss due to the phakic IOL. In other words, 1.5 and 2 percent assumed loss from the phakic IOLs were used as examples to then calculate the age when the cell density would be less than 1,200 cells per millimeter squared and less than 1,000. These ages, shown in the fourth and fifth columns, assume a surgical loss of 10 percent and compound the 1.5 and 2 percent loss annually.

Finally, in order to determine the minimum cell density inclusion criteria, we looked at the starting densities that would ensure greater than 1,000 cells at age 70 for the 21- to 25-age range, and at 75 for 26 and older.

So this table verifies that the minimum inclusion criteria, as shown on Table 1, would be sufficient in a worst case situation to allow for adequate cell density for the health of the cornea for roughly the life of the patient, assuming a 2 percent annual loss from

DR. SWANSON: Okay. That was a general point I was making on confidence intervals. You can say the number's 75 percent, but statistically, it could be anywhere from 40 percent to 100 percent, 99 percent, but I think you were going to comment on that.

DR. BANDEEN-ROCHE: Well, I did have a follow-up. I mean, you just made one of the points exactly and then a slightly more technical but maybe as important point is whether the statistical significance that you quoted in your presentation was for the whole sample of eyes. Did it account for correlation between eyes in any way? Do those results hold up if they're only done on the primary eye?

DR. PETTIT: The statistical significance, I'm sorry, in terms of which parameters?

DR. BANDEEN-ROCHE: The clinical findings of, for instance, slightly better contrast sensitivity in the Custom cohort compared to the conventional cohort. I believe your presentation at the end said that some of those clinical comparisons were significantly in favor of the Custom group. No confidence intervals were provided, they ultimately should be, but my question is did those statements of statistical significance incorporate the correlation between eyes in any way? Do they hold up when they're only done on the primary eye or am I mistaken all together? Was there no significance at all?

DR. PETTIT: There were statistically significant differences, and we did try to note those, but with regard to if we break it down by primary eye and whatnot, we haven't done that analysis.

DR. BANDEEN-ROCHE: And then, my very brief just to finish off my questions, in terms of your correlational response to Dr. Bradley's presentation forthcoming, I noticed that those were for the 6.5mm diameter. Did you do those on the 5mm diameter as well and what was the --

DR. PETTIT: They were comparable.

DR. BANDEEN-ROCHE: They were comparable?

DR. PETTIT: Yes. The numbers weren't exactly the same, but they were definitely very close.

DR. WEISS: Dr. Burns?

DR. BURNS: Yes. You talk about the difference for the undercorrection.

MS. THORNTON: Could you speak into the microphone, please?

DR. BURNS: I'm wondering if, when you talk about touching up the surgery, you're thinking in terms of now having less surgically-induced aberrations and whether you're going to try to deal with that on the touch-up or just do the spherical correction in the algorithm, and do you think that?

DR. PETTIT: Well, we're actually discussing with the agency the best way to address this in the commercial embodiment and also going forward. The data that I presented, the important thing to me was that with this algorithm, there's no -- some people call it coupling. When you try to treat a lower-order aberration, you actually induce wrong amounts of the higher-order aberration, and by showing that there was no significant coupling between the lower- and higher-order terms, you could envision, if we took out that .37 diopter on average defocus error, we aren't going to suddenly have lots more coma or lots more spherical aberration. So giving some adjustability or changing the target by a small amount, we're not going to totally disrupt the higher-order differences that we've seen. Does that answer your question?

DR. WEISS: A moderately phrased and lengthy question by Dr. Bullimore.

DR. BULLIMORE: Thank you, Madam Chairman. This is Mark Bullimore.

I would like to commend the sponsor on an excellent job. One of the dissatisfying things, though, about the data is that from this initial cohort of over 400 eyes, we're now presented with an efficacy cohort of a little over 100, a comparison cohort of 50 of which, if I'm

not misquoting the sponsor, fewer than 20 were treated with the most up-to-date algorithm, is that correct?

DR. PETTIT: Can I clarify that for you?

DR. BULLIMORE: Yes, please do for us.

DR. PETTIT: Okay. And I apologize. I know this is a little bit complicated.

DR. BULLIMORE: That's fine.

DR. PETTIT: Over the course of the trial or in the early parts of the trial, we were enrolling patients and randomizing, one eye Custom, one eye conventional. Now, the conventional surgery was a 6.5mm optical zone using the latest conventional algorithm, and that persisted throughout the entire trial. So all those patients were treated exactly the same.

The Custom algorithm evolved up to Level 7, as you indicated, and then all the 139 patients were treated with that in the Custom eye with that same algorithm. So the data that you have for the primary cohort, there were no adjustments, no site adjustability, nothing. They were all treated exactly the same with the single algorithm.

For comparison, looking at all the conventional eyes that we had enrolled in the contralateral arm of the study, we found that there were 50 eyes that met the inclusion criteria to be defined as spherical. So then, if you look at those two groups, on the Venn diagram, where do

those patients intersect? It turns out that there are 19 patients that were treated conventionally in one eye and with Algorithm 7 in the Custom eye. That's a very small sample set and the only reason we bring it up is that based on some reviews back and forth with the FDA, we did narrow it down because that's a pretty powerful group to look for differences. It's a small number, I concede, but we saw exactly the same wavefront trends and whatnot that we did in the much larger groups.

So it's small but it's a pretty good little set to look at to support what you find in the big set.

DR. BULLIMORE: Yes, I think there's a number of challenges that the panel's going to face later, but I want to sort of at least get them on the table during this session where you are essentially available to answer questions.

I think your data have shown reasonably compellingly or fairly compellingly that --

DR. PETTIT: Thank you.

DR. BULLIMORE: Let me tell you what you've shown first.

(Laughter.)

DR. BULLIMORE: That the aberrations in your Custom algorithm are lower than they are in the conventional algorithm and that's a given. But in terms of

what's communicated to the patient in terms of their vision expectations, they're still higher than they are preoperatively and that's something that somehow needs to be captured in the claims labeling, whatever, that we handle later.

There's a couple of contradictions in your data and they may be reasonably easy to explain, given the brainpower or horsepower around the table here. Aberrations are worse postoperatively than they are preoperatively, but there seems to be some modest or subtle improvement in the low contrast acuity and the contrast sensitivity data and that's something that again we have to somehow reconcile, even though the optics are getting worse but not as worse as they are with conventional, there seems to be some modest improvement in vision.

So those are the issues I'm wrestling with internally, are how to get that information out appropriately, and I've been looking through your patient information booklets and your physician booklets and you've done an admirable job.

DR. PETTIT: Thank you.

DR. BULLIMORE: But it's going to be awfully confusing to people because your information booklet is covering a range of procedures, a range of lasers, a range of algorithms, and even if these booklets make it to the

patient, the chances of them getting the right message is going to be difficult.

DR. PETTIT: I'm George Pettit with the sponsor again.

It's in our best interests to try to communicate realistically to the patients what's going to happen. We don't want unhappy postop patients certainly. So we look forward to your input and trying to present that in the best way we can.

The modest improvements in some of the low contrast, the BCVA and the contrast sensitivity that we see, Dr. Bradley in his review noted that and suggested two factors that may be contributing to those findings. Number 1. There is a slight magnification difference because the patients are best corrected before and after surgery, but they don't have nearly the degree of myopia after treatment, and the other thing is simply that they're familiar with the test. Maybe there's some aspect of it that they learned how to do better. So you know, I can't optically explain why we're seeing statistically significant improvements after treatment where we're increasing the higher-order aberrations, but in looking at the Custom versus conventional, I think the differences are still somewhat valid because whatever those, the learning effect or the magnification difference, that happens in

both sets of eyes. So you know, where is the absolute level? There is definitely some uncertainty and so we don't quite understand what's really going on there.

In other studies, contrast sensitivity with conventional LASIK, contrast sensitivity dips and it tends to come back near baseline and that's just for conventional treatment with our system or with other systems in published studies. So that's a real effect that's out there, but the fact that we see a difference and at least in the early time course, a fairly significant difference between the two populations, we think, is encouraging and supportive of the notion that Custom is better.

DR. WEISS: I just want to ask one simple question and then we're really running over and so we're going to close off the question session and this is simplistically. Are these people any happier than the people who have conventional treatment? You have 19 people and I sort of phrased that in a more scientific form. Did you ask the people? Did you do a survey? But if you didn't do a survey of the clinicians before us, what is your perception? Do these people notice the difference?

DR. PETTIT: Dan, before you all answer, can I just say? We're not going to be able to dig up the data on those specific 19 patients in any reasonable time frame this morning.

DR. WEISS: Okay. That's fine. Then perceptually, does a patient notice if they've had this customized treatment versus if they had conventional treatment?

DR. DURRIE: Very difficult to answer, and I want to tell you why, because this residual myopia issue kind of clouds it because one thing we know as we go back to look at the patients who had quality night driving problems dissatisfaction, those are the ones that have residual myopia.

DR. WEISS: What about if you took out the ones with residual myopia? Eliminate those residual myopia. The remaining 10 people you've got, are they any happier?

DR. BRINT: It's three. Three people.

DR. DURRIE: Yes, I think it just gets so small, and it's one of those things where I've asked the same question because it's obviously one of the things I want to know what to tell my patients. So it's the first question you asked today and it's the one that we're --

DR. WEISS: Well, of course, this is the basic question because otherwise, what are we talking about? Otherwise it's just numbers.

DR. DURRIE: Well, I think the contrast sensitivity and low contrast acuity is very important to me because I've been studying contrast sensitivity for quite

awhile. I've done a lot of clinical trials on a lot of different devices, and I've always seen that we were losing contrast sensitivity.

DR. WEISS: I'm going to just, in the interest of time, go back to if a patient doesn't notice it, it might be important, but ultimately the patient's going to decide if this was worthwhile or not.

DR. DURRIE: And that's what I was getting at, is that, this is what I'm hearing from patients, you know, is that their quality of vision is better. I know that that's a soft thing, but this is what I'm hearing. We can get everybody out of glasses but now working on quality and as we're looking at these new technologies, I think that's where we're heading up the scale, but I do not have the statistics because the sample sizes are too small to answer the question.

DR. WEISS: I'm just asking you your perception is of those number of people who ended up not undercorrected, their customized eye, they preferred to their not customized eye or we don't know that?

DR. DURRIE: I can't answer that.

DR. BRINT: Steve Brint.

I think you're asking for an anecdotal answer, and I'll give you an anecdotal answer.

DR. WEISS: If that's all I can get, that's

better than nothing.

DR. BRINT: I did 19 of the eyes. Again, this includes the astigmatic group and I don't know how many of those ended up in the spherical-only group. Nineteen eyes in the contralateral study, so that one eye had the Custom and one eye had the traditional, and I just sort of know from looking at the data that I had, my site had the smallest amount of undercorrection, and I strongly feel that the patients that had the custom ablation appreciate the improved quality of vision, and a lot of those, I don't know exactly how many, but when we look at those patients that had improved best-corrected vision to 20/12 or 20/16, some of those are in my patient group and I definitely feel that they can appreciate the improved quality of vision, the sharpness and, you know, I hear anecdotally things, I have bionic eyes and this sort of thing.

So I think it's a real phenomenon and as we're able to go back and manually find the method of tweaking that nomogram or adjustment to have the lasers specifically tailored for each of our individual sites and humidity and temperature conditions and these things as we normally do, that this is going to become even a very much more real phenomenon.

DR. HAKIM: Omar Hakim.

Among the patients i treated were three

exercise to see what our limits are, maximum and minimum unacceptable rates of cell loss.

I've approached this argument by first looking at life expectancy data. The RP-2000 mortality table is based on a study of the mortality experience of pension plans conducted by the Society of Actuaries and was in response to pension legislation that directed the Secretary of Treasury to promulgate the use of updated mortality tables for various pension calculation purposes.

According to that table, the life expectancy for a 21-year-old male is 58 future years or an age of death of 79. The life expectancy for a 21-year-old female is 62 future years, so an age of death of 83. Those are United States data.

Realize that depending on your entry date, you'll have change, obviously, to your age of death. If you enter at age of 80, you don't have an age of death of 79.

(Laughter.)

DR. GRIMMETT: But I used it as a fixed value for this particular analysis, so as to not get confused with multiple iterations of the tables. Suffice it to say that when you enter at 20, 30, or 40, it may only differ by a few years in terms of your age of death.

The minimal acceptable corneal endothelial cell

important, but if you look at page 22, you've given symptoms that the patients have postop for custom ablation, and I asked previously for the same data to be given for conventional treatment so we can look at numbers rather than anecdotal information about the degree of complaints that you got about glare, halos and night driving, et cetera, and then on page 23, patient satisfaction, you give it to us for custom ablation. We don't have it for conventional ablation. I'd like to see that so we can compare.

Now, the problem with that is that you have patients enrolled in your custom ablation who had extremely high expectations and so you didn't control preoperatively for the level of expectation and that is going to skew your patient satisfaction, but still I would like to see that information for conventional to compare to your custom ablation patients.

DR. WEISS: If you can answer in one sentence or less, if you have it available? Actually, do you have any of this available or can it become available today?

DR. PETTIT: No.

DR. WEISS: No. Okay.

DR. PETTIT: But we'd be happy to provide it.

DR. WEISS: When it becomes available at another time but not at today's meeting.

Okay. I'd like to thank the sponsor very much for an excellent presentation and for their helpful answers.

We're going to go on to the FDA presentation. The FDA will come up to the podium now.

Dr. Beers, will you begin?

DR. BEERS: I'm Everette Beers, Chief of the Diagnostic and Surgical Devices Branch of the Division of Ophthalmic and EMT Devices.

I'm going to turn this over to Jan Callaway, the team leader, but before I do, I wanted to really say thank you, Jan and the rest of the team, for getting this together and to panel so quickly and also to the cooperation from the sponsor for meeting some very tight deadlines.

Jan?

MS. CALLAWAY: On November 2nd, 1998, an original PMA application, P970043, the LADARVision Excimer Laser System, received approval for its argon fluoride excimer laser. The device was intended for use in photorefractive keratectomy, PRK, to correct mild to moderate myopia with astigmatism. On May 9th, 2000, the laser was approved for the expanded indication of laser-assisted in situ keratomileusis, LASIK, for myopia with or without astigmatism, and on September 22nd, 2000, for LASIK

for hyperopic astigmatism and mixed astigmatism. The laser uses a small diameter pulsed ultraviolet laser beam to reshape the cornea and incorporates an infrared eye-tracking system.

In Supplement 10, the sponsor's requesting approval to further expand the indication statement for wavefront-guided LASIK correction for the reduction or elimination of myopia up to 7 diopters with less than .5 diopters of astigmatism at the spectacle plane. In the clinical studies supporting this application, the method by which the planned ablation pattern is determined has been modified, not the ablation technology. The pulse energy, firing rate, influence distribution at the treatment plane, and eye-tracking hardware and software are the same as for conventional LASIK treatments. In the previously approved system, the ablation pattern was based upon manually entered manifest subjective refraction data for sphere and cylinder. The CustomCornea ablative shaping algorithm utilizes information that is obtained from a wavefront measurement device. Wavefront sensing provides a detailed refractive map, including sphere, cylinder, and higher-order aberrations, unique for each eye. A computer file containing this information is transferred to the treatment laser. The ablation profile is calculated directly from wavefront data.

The FDA team responsible for Supplement 10 included Dr. Bruce Drum, Dr. Malvina Eydelman, Dr. Gene Hilmantel, Dr. Dexiu Shi, Dr. Marwood Ediger, Dr. Lilly Yue, Dr. Jean Toth-Allen, Ms. Mary Lou Davis and myself. Dr. Drum will not present the areas in which your input is being requested.

DR. DRUM: Thank you, Jan.

Since we've just gone over the submission in substantial detail and we've gotten an excellent presentation from the sponsor, I'm not going to go into specifics with regard to the study itself, but I'll mainly concentrate on questions that we have that we would like the panel to address.

Jan has just named the review team, and I'll go right to the introduction. Dr. Eydelman's clinical review did not come up with specific clinical questions for the panel. The data appear to be satisfactory with regard to basic safety and effectiveness, but this is the first submission of its kind for trying to correct higher-order aberrations, and so we have several issues that we would like to have the panel address with respect to any special information that would be required to evaluate the results of higher-order aberration treatment, and for the most part, these will involve perhaps special analyses or information that may be helpful in determining the proper

labeling.

First, we've already gone over this, the comparison study, but I'd like to remind the panel of the study and the issues that were involved in it, and the comparison of the results showed that the Custom eyes were slightly better than the conventional eyes in a number of aspects. The higher-order aberrations increased less for the Custom eyes than for the conventional eyes, and there were absolute reductions in aberrations for a higher percentage of Custom eyes versus the conventional eyes and that may be an area that would be beneficial to investigate further. That would be information that patients might find useful in deciding whether to have the procedure.

As George has already told you, we've tried to find a way to evaluate the higher-order aberrations that was interpretable in terms of more people might be familiar with and relating the improvement of vision to the equivalent spherical blur, and there was a little less than a quarter of a diopter effective reduction according to the procedure that they've worked out.

Relative to preop, the postop contrast sensitivity was higher for Custom eyes than for conventional eyes only by a small amount on average, and so basically what I'd like to ask the panel, what differences between Custom and conventional outcomes are clinically

under functionally significant, given that the differences are typically small, and what labeling claims would be supported by these differences? Also, are any additional clinical data or analyses or criteria needed to evaluate the relative effectiveness of Custom and conventional treatments?

I won't dwell on this. George has already given you a very clear presentation of how higher-order aberrations are analyzed. One thing I might mention, you can do RMS analyses of the overall correction or on a term-by-term basis, and I guess the question there is is that an adequate way to look at the effectiveness of reducing higher-order aberrations or might we need some other additional methods?

Just some thoughts about the analysis of higher-order aberrations. The functional significance is not always evident, but if you look at the pictures of various Zernike terms of the higher-order aberrations, you see different spatial patterns, that you have coma and you have spherical aberration and then you have these other terms with little scallops around the edge, and it's not always clear, it's not clear at least to the general populous, what those mean in terms of vision. So if there's a way that we can make that clearer or find out which aberrations to pay attention to that would be

helpful. Different Zernike terms are the same. RMS may have different visual effects. That's been alluded to earlier. Elimination of all aberrations may not be optimal. There's evidence that some positive spherical aberration may be beneficial for equivalent defocus or for accommodation or other visually important functions.

It would it be beneficial to ask for an analysis of vision not assuming that a zero aberration is optimal? There's also positive and negative spherical aberration. Would it be valuable to separate the analysis of how the spherical aberration is changing? Zernike parameters depend on pupil size. When you do a Zernike analysis of higher-order aberrations, the coordinate system is defined by the limits of the pupil. So if you have a 4mm pupil, all of your Zernike terms are defined on a 4mm space. If you have a 7mm pupil, they're defined on a 7mm diameter and the same term will mean a different thing, and is there a way to take that into account when we're evaluating the effects of correcting aberrations assuming that certain pupil size -- when the pupil actually is taking on a whole range of sizes in real life?

The last point. Can higher-order aberrations be compared to equivalent defocus? We've made a first step with the sponsor at trying to find a way to relate higher-order aberrations to defocus, but you might have some

suggestions about how that could be improved. So the basic question here is what information about measurement analysis and correction of higher-order aberrations is needed in the labeling to inform physicians and patients about the safety and effectiveness of CustomCornea treatments?

One additional specific area that has already been addressed to some extent is stability, refractive stability. We have a list of criteria by which we define refractive stability for sphere and cylinder. I won't read them all, but basically it's just making sure that the change of refraction goes at least towards zero over time or that the rate of change goes toward zero and that it ends up close to your target.

But most of these criteria, they don't directly address the kinds of changes that are probably going to take place in higher-order aberrations. In other words, if your higher-order aberrations are changing, standard stability criteria will not detect that. You may need special analyses, such as looking at changes in RMS over time, and that raises a question of whether a reduction in RMS is adequate to define stability or whether there may be changes taking place that RMS analysis in insensitive to.

George Pettit has already given an answer to the question of whether the stability of sphere and

cylinder may interact with the stability of higher-order aberrations and concluded that they were not helpful, but I'm not sure that we should take that as a final answer because he based that on a correlation analysis of a fairly small number of eyes. So I'd still appreciate your input about whether we need to relook at our stability criteria in the case of a higher-order aberration treatment.

I guess that's all I have for now. I have some additional slides with individual questions on them for when the panel is making a decision.

Thank you.

DR. WEISS: Are there any questions from the panel for Dr. Drum or any other members of the agency on the presentation?

Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: Just one clarifying question about the RMS. When you get term-by-term RMS, is that essentially equivalent to the absolute Zernike coefficient or does it also include information about the basis functions?

DR. DRUM: Well, I can't give you a really confident answer here, we have people that are more expert than I am on the Zernike analysis, but it seems to me that if you look at the RMS of an individual Zernike term, the shape of that term is defined. So a reduction in RMS for

that term would probably be a fairly strong indication that that variability or that the size of that term is reduced.

Having said that, though, Zernike analysis is a polynomial expansion, and so all these terms are just picking out the part of the variation that fits the shape of that term, and they're all approximations and so you can't get a really good description of what's going on without looking at more terms. But perhaps Steve or Arthur would have a more intelligent answer.

DR. WEISS: I think we probably can deal with that in deliberations, and if there are no other questions, I want to thank you, Dr. Drum, for your presentation and thank the FDA for such a clear review.

We have five minutes for additional comments from the sponsor, if they would like to make them, they can come up to the podium, and then we will break for lunch.

Does the sponsor have any comments they would like to make? I take that as a maybe, a firm maybe. That's a yes.

DR. PETTIT: Just real quick.

We were able to pull one answer to one question that was asked earlier. For the spherical eyes in the Custom cohort, the mean pupil mesopic pupil diameter was 5.63mm with a standard deviation of .89, and for the comparative 50-eye conventional cohort, it was 5.78 plus or

minus .081.

DR. WEISS: Can you repeat that again?

DR. PETTIT: Okay. The mean pupil diameter for our primary cohort was 5.63 in the Custom eye and 5.78 in the conventional eyes, and the standard deviations were .89 and .81 for those two groups, just to answer a question that came up earlier.

DR. WEISS: Fine. No questions on our side. Questions on their side?

DR. BULLIMORE: Can you just remind us what the optical diameter is, optical zone diameter?

DR. PETTIT: In all treatments, the optical zone diameter was 6.5mm.

DR. WEISS: If there are no other questions from the sponsor, Sally Thornton has two announcements.

MS. THORNTON: I have just two things. There is a FedEx package at the registration desk for a Helen Laurielle, L-A-U-R-I-E-L-L-E, of Staar Surgical, and the panel members and the FDA staff have reservations at the Tack Room of the hotel restaurant.

DR. WEISS: Important announcements as we're going to break for lunch. So I have 12:00 now. I would ask everyone to be seated and ready to go at 1:00.

(Whereupon, at 12:00 p.m., the meeting was recessed for lunch, to reconvene at 1:00 p.m.)

AFTERNOON SESSION (1:02 p.m.)

DR. WEISS: Could the members of the panel please be seated?

MS. THORNTON: Before we start, I'm doing what you told me to do, I have an announcement I'd like to make to the panel, the sponsor, and the FDA, who may be wanting to speak in the microphone. The transcriber and summary writer and the audio folks have asked me to ask you to please do not be any farther away from the head of the microphone than four inches. It can't capture it if you don't get within that short space and please speak directly into it. They can't get it when it's like this. They can't get it when it's like that either. So I'd just like you to be aware of this, so that we can get an accurate transcription and make their job a lot easier. They can't turn up the audio but so far or it'll start to squeal. So please help them with this.

Thank you.

DR. WEISS: Okay. Well, we will begin again at this point with the committee deliberations and the primary panel reviews. We're going to start with Dr. Andrew Huang for his review.

Thank you.

DR. HUANG: Good afternoon, ladies and gentlemen. I'm sure by now the members of the panel and

the sponsor should have my written review. So I'm not going to repeat what I have written, but basically I would like to address to the public as well as the panel of the members, the members of the panel, that there are some philosophical points as well as some specific questions.

First, as we all know, the existing refractive surgery, such as LASIK or PRK, can treat sphere and cylinder, and it doesn't really treat higher-order aberrations. However, with this new wavefront technology, we can now measure these high-order aberrations and begin to treat them.

Nonetheless, whether this technology will work in practice is another question all together. As we all know, vision is really a dynamic process. The patient will have dynamic variations and a patient may have a different accommodative state throughout the day and throughout the week, and using a wavefront technology to correct the vision at one given point, as indicated by the sponsor, may not be adequate for those patients, especially for those people that need night vision or the patient performing the task in the dark.

There's a common statement that we often heard for this kind of patient. That is, is 20/20 for 10 to 20 years better than 20/15 for two to five years using that new technology?

Suffice it to say that about 90 percent of all aberrations are low-order aberrations. Either they are sphere or cylindrical, such as myopia, hyperopia, or astigmatism, and I believe the conventional or the existing LASIK is probably adequate for most of these patients.

There are up to about 10 percent of the patients have much higher-order aberrations and these patients probably will benefit greatly from the use of this wavefront technology. So therefore, using this technology will enable us to pick up these specific aberrations and to treat them accordingly with confidence and also ensure the safety as well as the quality of vision.

For patients with good preexisting low refractive error or good preop vision, they may already have their very, very minimum aberrations and potential benefits of the Custom wavefront-guided surgery probably will be very, very small. They do not necessarily need better supervision and the wavefront technology at best is probably for us to ensure the safety as well as the quality of their vision. However, if we can selectively use the technology to select the patients with specific amounts of higher-order aberrations and treat them accordingly, the benefit of custom ablation probably can be further justified.

Specifically for the sponsor and also for the

public, I found the study is very well conducted and the sponsor should be commended for their efforts for this accountability of their entire dataset.

However, the small cohort has been discussed earlier today. There are only 179 patients and specifically that in the 70-data cohort, there were only 19 patients ranged from zero to -1 diopter and nine patients went from -6 to -7 out of these 426 eyes. For the effectiveness data, out of 139 eyes, there were only one eye in the group of zero to -1 diopter and four eyes in the -6 to -7 diopters. So I found this small number of data is unacceptable or insufficient for this review.

There's also a general trend towards undercorrection, and we have discussed earlier and also answered by the sponsor regarding the future management of this treatment, but I would like to raise the question to the panel members, if we should need further data before we recommend final approval?

The third point is that in both groups, the conventional treatment versus the CustomCornea treatment group, showed a reduction of total aberrations. As expected, both groups substantially reduced the preop low-order aberrations. Nonetheless, high-order aberrations were generally increased and we have discussed this earlier today. The CustomCornea did not result in less overall

higher-order aberrations than the conventional treatment. Specifically, the spherical aberrations is only increased by 22 percent in the CustomCornea and by about 80 percent in the conventional LASIK, and I'm not aware of the clinical significance of this kind of difference.

The fourth point is that the inverse correlation was the low contrast best-corrected visual acuity and the total higher-order aberrations was at best modest. The correlation coefficients was less than .5. There was no strong evidence suggesting that the higher-order aberrations were further corrected with sustaining effect on the major improvement by CustomCornea. Specifically, about 20 percent of the patients had decreased vision greater than one line in their best-corrected visual acuity, suggesting that no additional treatment was really benefit from this CustomCornea.

The fifth point is that the patients on postoperative questionnaires, there were 40 items raised. There were seven of them, 10 percent or greater of the patients, answer was worse or significantly worse than their preoperative finding. I found it was significantly higher percentage of the dissatisfied patient in this cohort and maybe preoperative and postoperative counseling should be included in this type of clinical study.

And finally, I would like to emphasize there is

no data in this current submission that on the long-term stability beyond six months and there's also no follow-up on the retreatment, even though there was some anecdotal data. So therefore, the long-term effect and the necessity of retreatment cannot be ascertained in this proposal.

Thank you.

DR. WEISS: Thank you, Dr. Huang.

We will have our second panel reviewer, Dr. Bradley, speak.

DR. BRADLEY: Thank you.

I'd perhaps reiterate what some of the other panel members have already said today, and that is the presentation by the sponsor and the data provided by the sponsor were really excellent in my opinion and that helped with the review of this PMA.

I'm going to cover several issues here, start out with the standard ones that we on the panel are concerned about, efficacy, stability, safety, and using standard criteria for these, before really getting into the specific issue associated with the current technology and that is one of aberration correction and obviously the challenging issue of how to label this product.

As most of us in the room are aware, the level of understanding of the optics of aberrations and the visual ramifications of these aberrations is imperfect and

the level of expertise in this room is high. For the average physician, the average patient, this is going to be a huge challenge and one that the FDA and the sponsor and the panel must come to some conclusion on.

By the way, there's something else going on today, and that is I'm a Mac user, and the question is can a Mac user effectively use a PC? There's an ad on TV at the moment that says that PC users can convert to Macs quite easily. So this is a test of whether a Mac user can convert to a PC. So let's see what happens. Let's try that button. Great.

I put this slide in because I think it's very important to get an overall picture of what's going on here. First of all, there are really two innovations here and they have been blended into one as the discussion has gone so far today, and I wanted to separate them out. First off, the current wavefront-guided LASIK procedure is employed what I call our projective optical measure to control the laser ablation. This is unique in that previous approaches have always been to employ subjective refraction, and it's worth pointing out that prior to this technology, typical objective measures of optical status of the eye, for example, autorefractors, are used only as approximations, later to be refined by subjective refraction. So going straight to guiding the laser using

an objective device is really novel in and of itself, irrespective of the fact that they're trying to correct high-order aberrations. They're using this to try and correct regular sphere and cyl, and I think that's an innovation to be fully aware of.

Second, of course, is that in this particular device, they're trying to go beyond correction of sphere and cyl to correct the higher-order as they're known aberrations. This poses a unique challenge again, not because there's anything uniquely different about a higher-order aberration versus a lower-order aberration, but primarily because the higher-order aberrations are much, much smaller. So the challenge here is can they correct very small aberrations, very small imperfections in the optics of the eye, rather than the larger myopias or hyperopias that they're typically trying to correct? So I think those are two types of innovations here and both are worthy of our appreciation.

The efficacy. A couple of criteria we always examine for efficacy. Basically, this is a procedure to correct refractive error. That's why the patients are in there. How well does it do? Obviously the way to examine that is to look at the postprocedure refractive error distribution, and I've always preferred to see the data in this format as provided by the sponsor and we saw it this

morning. This is a scattergram of post versus pre refractive error in terms of spherical equivalent, and this is meant to be the Y equals X line. That is, achieved versus attempted. I'm sorry. This is achieved versus attempted, and the data should fall along this line, solid line in the middle, if the achieved equals the attempted, and these people will end up emmetropia. I think the attempted was to correct for emmetropia.

This distribution looks good, if not better, than many we've seen before, many published in the literature for other lasers, other procedures. I just highlighted a couple of these outliers up here who have been between 5.5 and 6.5 diopters of myopia, clearly undercorrected by up to about 2 diopters, it appears, and again that's been commented on already today. By and large, this dataset looks as good, if not better, than what we've seen before.

The FDA actually set some standards for this or some guidelines. They wanted to know how many eyes have less than or equal to half a diopter refractive error post-LASIK. The FDA requires at least 50 percent, and in this PMA, we see 75 percent. Likewise, for 1 diopter of post-LASIK refractive error, the FDA requires that at least 75 percent achieve this, and in this PMA, it's almost 100 percent, up to 96 percent. So that looks very good. It

clearly meets the FDA guidelines, comfortably meets them.

Other effectiveness criteria is the post-LASIK uncorrected visual acuity, and as we all know, this will correlate highly with the post-LASIK refractive error, and the FDA sets a standard here that 85 percent must have an acuity better or equal to 20/40. It turns out 99 percent of these patients had that. The sponsor also provided us with this criteria. What percent of the patients had better or equal to 20/20 acuity? It turns out 80 percent of these had that. Remember this is uncorrected, and I think those 80 percent probably consider the procedure to be effective.

Issue of stability is always there, primarily sort of a historical concern in that this sort of regression that was very large in the early procedures, slowly regressions are becoming smaller and smaller, and this is the classic sort of plot. This is the refractive error pre is the mean. This is post at one month, post at three months, post at six months. The difference between the three- and six-month data is basically three-hundredths of a diopter. Essentially, it achieved perfect stability in terms of the mean.

We're always interested, though, about outliers as opposed to just the mean, and the FDA actually has some guidelines on that. They want less than 5 percent to drift

by more than 1 diopter and between the three-month and six-month, and it turns out none of them did in this particular PMA. So again, I think they've established stability quite nicely.

Safety issues. There are lots of people in the room far more qualified than myself to assess adverse outcomes and other types of what I might term pathological outcomes that would be safety issues. I've concentrated here on what I consider to be the general overall safety guideline and that is best spectacle-corrected visual acuity, the idea being is that if the optics subsequent to the procedure are in good shape, you ought to be able to correct this patient to have very good acuity. So this is our benchmark safety criteria, and again the FDA has certain guidelines for this. They want postop, the best-corrected, how many patients are going to be allowed to be worse than 20/40. The FDA guideline is only 1 percent. There was zero in this PMA. Also, the FDA says, well, how many can lose greater than two lines? They allow 5 percent. Turns out it was less than .5 percent in this PMA. So they're exceeding the FDA guideline by a factor of 10.

Some other data which I thought were quite important on this issue, the best spectacle-corrected visual acuity preop, what proportion of the eyes had better

than or equal to 20/20 acuity? It's 99.3. Postop, 99.5. Basically the same. Interestingly, postop, best spectacle-corrected visual acuity, better than or equal to 20/25, was every single eye, and so with this criteria, clearly the PMA has demonstrated safety.

Now, let's move on to aberrations. This is a tricky area. So let's just summarize a couple of points. The wavefront-guided LASIK results in lower levels of higher-order aberrations than conventional LASIK. This was the comparison cohort that we saw. Some concern about the sample size here, but clearly when you compare the conventional against wavefront-guided, wavefront-guided eyes ended up with lower levels of higher-order aberrations than the conventional LASIK. This improved outcome of wavefront-guided LASIK may and is likely to account for the small differences seen in best-corrected visual performance when compared to the conventional cohort.

Some question has been raised this morning about, well, how significant is this reduction in higher-order aberrations, and I'm not sure that the scientific literature can answer that question, and the sponsor's data may have to suffice to answer this, and what we saw this morning is that there were these slight improvements in the best-corrected visual performance of the wavefront-guided LASIK group compared to the conventional cohort, and again

that is probably a reflection of the fact that the higher-order aberrations were lower in this wavefront-guided group. Very important thing to point, though, Number 3, wavefront-guided LASIK procedure increased the level of higher-order aberrations relative to the preop levels. This is an extremely important point to keep in mind. So I think those are the three main points that I'd like to make about aberrations.

Let's move on to labeling, and I personally think this is the greatest challenge for us today, and I'm not sure I have any clear conclusions in my own mind at this point. So let's see how the afternoon goes.

Number 1. I think it must be clearly stated that wavefront-guided LASIK does not reduce the level of higher-order monochromatic aberrations relative to preop. Thus, in no way can wavefront-guided LASIK be thought of as a procedure to correct higher-order aberrations and render super-normal vision. This is an extremely important point.

Number 2. I do believe, though, the sponsor can comfortable promote this new procedure as a new LASIK procedure that is an improvement, albeit slight, over previous conventional LASIK, and I think those are issues that need to be addressed in labeling.

More on labeling. Now we get into really the subtleties, and I say that to, let's say, we're stepping

down on the importance of the issue, but I think this is an important one. The sponsor in the PMA uses the term "CustomCornea" and I think the idea is a very attractive one, the idea being that as a patient, you go in to have your eye examined and using the wavefront measurement device, they are able to identify that your eye has a certain level of aberration and that includes myopia, astigmatism, spherical aberration, coma, and a variety of other terms, and it is now possible to sculpt the cornea to correct for your inherent optical problems, and therefore they're creating a Custom cornea to correct for the optical problems of your whole eye. It's a very, very attractive idea, and as the sponsor knows, in my original review, I challenged them to present some evidence that they had really achieved this.

Now, this challenge would never have originated if the post-LASIK aberration levels were lower than the pre, and if that were the case, we would have to conclude that they had corrected some, if not all, of the existing aberrations in the eye. However, as we now know, the postop monochromatic aberrations are actually larger than the preop. So it becomes a slightly tricky issue to establish whether or not the inherent aberrations of the eye have indeed been corrected. So given that complication about trying to ascertain whether or not the aberrations of

the eye have been corrected, a discussion really revolves around some correlational analysis, and there are two types of correlational analysis that can be done and the sponsor has done this.

One is pre versus post correlation, the idea being a very, very simple one, that if one had corrected the inherent aberrations of an eye, the aberrations that exist postop would be unrelated to the aberrations that exist preop. They would not correlate and that's what I said here. The pre versus post correlation you expect to be zero if individual aberrations, individual eye aberrations are perfectly corrected. You expect it, however, to be a correlation of one if they are left uncorrected. That is, if you have a certain level of aberration pre, you would have it post, and so we'd expect the correlation of one.

Interesting thing is that that correlation of one would only be expected if there is no variability in the measurements. That is, there's no test/retest variability. If there is test/retest variability, then this correlation of one would drop to somewhere between zero and one. That is, in the end, correlations between zero and one could be due to partial correction of the inherent aberrations of the eye or simply due to test/retest variability, and it turns out that's where the data lie, and the largest

correlations were observed here for the oblique secondary astigmatism, R was .46 for spherical aberration, it was .45, and this is just a scattergram showing the oblique secondary astigmatism, and there's the regression through the data, and again if the aberrations had not been corrected, but there was test/retest variability, we would expect a positive correlation with an R of less than 1.

So we're left not knowing whether this correlation, this positive correlation is due to either a failure to correct the aberrations of the eye or is simply, yes, due to a failure to correct the aberrations of the eye or only partial correction, and in order to assess that, we really need to examine the test/retest variability to know how effective the CustomCornea correction is, and I would certainly defer to our statistician to assess how we formally do this, but I think that can be done.

The second correlation or analysis that the sponsor performed, which I think was really quite instructive, and that is to correlate the intended aberration change versus the achieved aberration change. Now, the question here is very simple. If you've achieved what you intended, you can get a very good correlation, expected correlation of plus one, if the CustomCornea is perfect and there is no test/retest variability and an R of zero if it is completely ineffective.

Well, it turns out that you get an R of greater than .5 for the third order coma and trifoil aberrations, indicating that the intended was highly correlated with the achieved, indicating that some successful correction has occurred. Interestingly, the fourth-order aberrations, the Rs tended to be quite low, less than .5, indicating perhaps that they have not been effectively corrected. One interesting comparison can be made, if you compare what I've just shown you, and that is intended versus the achieved change, if that R is less than the pre versus post R, then I think we have evidence that the correction has not been achieved, and it turns out that was the case for Z4 zero and Z4 -2. Again, the statistician might be able to comment on that. So I think the evidence that wavefront-guided LASIK does a better job of correcting third-order than fourth is definitely there and there is some question of whether it corrects the fourth-order aberrations at all.

The final point, I think, visual benefits for correcting higher-order aberrations. This is a tricky one, very tricky one. It's tricky in the sense that science is a bit behind the sponsor in this case. We don't know all of the visual ramifications of monochromatic aberrations. Those data are now being collected in my lab and in other labs. So we're sort of at the cutting edge of our

scientific knowledge here, going a bit beyond it really.

A couple of points. Wavefront-guided LASIK is designed to correct monochromatic aberrations, but vision is in a polychromatic world. This is a very important point. So even if you correct all the monochromatic aberrations, you do not have perfect vision because you have chromatic aberrations. Just to put things in a bit of a perspective, Thibos and colleagues looked at a large sample, looked at higher-order monochromatic aberrations and found that they gave an RMS that is less than a quarter of a diopter. So the effects in dioptric terms, just like the sponsor has suggested, are less than a quarter of a diopter. That's sort of an equivalent based upon RMS, and I think Dr. Drum questioned whether an RMS comparison is appropriate.

Yoon and Williams recently published very nice data where they used wavefront correction in the lab, not on the cornea, they used an optical device to do this, and I've said perfectly correcting for higher-order aberrations. When they did this, again correcting monochromatic aberrations, but they're in a polychromatic world, they still found an improvement in visual acuity by a factor of 1.4 which is .15 log units or 1.5 lines on a logMAR chart, should convert a 20/20 to a 20/14, and this is basically the best you can possibly expect to achieve by

correcting monochromatic aberrations.

It's also worth pointing out there are some possible concerns that correcting monochromatic aberrations might compromise vision. This is again sort of at the edge of what we know here, but there has been some indication that aberrations are valuable in helping us control accommodation and certainly if you examine laser safety standards, these are based upon point spread functions in the eye that are spread out because of aberrations and therefore the actual flux density at the peak of the point spread function is reduced. If you correct the aberrations, these flux densities will go up because the point spread function will become smaller. So there's some general concerns about that.

I'll skip over that. Just in summary, the wavefront-guided LASIK system that we're examining here has met the efficacy, stability, and safety guidelines used by the FDA, and it appears to be an improvement over the already-approved conventional LADAR System. So I think in that sense, that is a pretty clear result. The questions regarding labeling, how well does the wavefront-guided system actually correct the monochromatic aberrations of individual eyes? This is still unclear to me, and again the sponsor and all of us really face the difficult challenge of communicating the potential visual benefits of

introducing less higher-order aberrations.

Thank you very much.

DR. WEISS: Thank you very much, Dr. Bradley.

Dr. Bandeen-Roche, did you want to comment on any of the statistics that were referred to?

DR. BANDEEN-ROCHE: This is Dr. Bandeen-Roche.

My overall comment would be that I agree with Dr. Bradley's presentation. I find his discussion of the statistics to be sound. Certainly his point about the correlation being dependent both on the strength of the actual relationship measured without any error and of the degree of test/retest reliability is right on, and there are statistics that can at least model the degree of attenuation in the relationship from the true relationship if one does know the test/retest reliability.

Then finally, in terms of the point of the correlation between intended and achieved with respect to the fourth-order being less than the correlation between pre and post RMS, I would certainly agree that it's inconsistent to cite one as evidence for no relationship and the other for evidence of a relationship, given that the directionality is reverse than what you would expect if that were true.

DR. WEISS: Thank you.

We're going to proceed with the panel

discussion of this PMA, and I would suggest that we go through the FDA questions one by one. Thank you very much, Dr. Drum, if you'd be so kind as to show us the question, and we can begin the discussion on those. We'll be starting with Question Number 1.

DR. DRUM: Let me see if I can open this.

DR. WEISS: Perhaps I can read this while we're getting it on the board and we can start the discussion.

The first question, which is on page 5 of the handout from the FDA, is what differences (if any) between Custom and conventional outcomes are clinically and/or functionally significant? What labeling claims are supported by these differences?" So what differences are clinically significant between Custom and conventional outcomes?

Would anyone like to start the discussion of this?

DR. BULLIMORE: I'll take a shot. Mark Bullimore.

Just to reiterate what Dr. Bradley said, I think the sponsor has shown fairly convincingly that the objectively measured aberrations with the Custom algorithm device are significantly less than those obtained with conventional LASIK. The caveat, of course, is that both procedures increase the level of aberrations over and above

what you would expect preoperatively.

DR. WEISS: How would you address the question functionally significant?

DR. BULLIMORE: I was hoping somebody else would address that. I mean, if you want me to put something into words, I would say that in the labeling and patient information booklet, that these demonstrated improvements in the aberrations over conventional LASIK may lead to a modest improvement in some aspects of patient's vision.

DR. WEISS: Sufficiently nebulous.

DR. BULLIMORE: Thank you. That's high praise.

DR. DURRIE: Are you running for office next?

Dr. Matoba?

DR. MATOBA: This patient information booklet that's in our -- is this the updated version of the patient information booklet? Because all it says here is under "What Are the Benefits of CustomCornea LASIK?," all it says is, "CustomCornea LASIK surgery may reduce overall nearsightedness. CustomCornea LASIK may also reduce or eliminate the need to wear glasses or contact lenses to see clearly." Is that all you're going to claim then?

DR. WEISS: Someone from the sponsor can approach the podium and perhaps give a succinct answer. It's actually quite a simple question. The insert we have

for patient information, is that the final insert that was given to the FDA, and obviously we can ascribe some changes that we would suggest, but I think Dr. Matoba wanted to make sure that there wasn't anything more updated in terms of what you were going to convey to the patient.

DR. MATOBA: Because if that's all they want to say, I don't think we necessarily have to suggest that they say more.

DR. WEISS: Yes, please?

DR. PETTIT: Okay. The version that you have, I understand, was before the latest round of response to deficiencies, and I guess we were waiting for feedback from the agency and from the panel as to what would be appropriate beyond those very simple remarks to put in there.

DR. WEISS: Fine. Thank you very much.

So we have Dr. Bullimore suggesting that we put in further comments elucidating the potential advantages and Dr. Matoba suggests perhaps we should leave things as it is in the present insert.

Dr. Bullimore?

DR. BULLIMORE: And a philosophical question for the panel is whether we think there should be an attempt to describe and demonstrate to a patient what the benefits might be and include fancy diagrams and simulated

eye charts or whether, you know, we should steer the agency and the sponsor towards some simple statements about, you know, proven superior optical quality that may lead to some modest benefits, visual benefits in certain conditions.

I mean, we can go either way, I see it. We can keep it very nebulous, I think that was your word you used to describe my previous statement, or we could make the suggestion that, you know, there's a couple of chapters out of an optics and vision science textbook included in the patient information booklet.

DR. WEISS: You know, I'm going to ask actually just a simple question to the panel just in terms of polling panel members. If you could raise your hand, if you believe that CustomCornea ablation has a clinically and/or functionally significant improved outcome over conventional LASIK? Why don't we start there? And then after that, we can decide how we might pen that.

The members of the panel, who here, if you could raise your hand, if you feel from the data presented that Custom ablation has a clinically or functionally significantly improved outcome over conventional treatment?

(Show of hands.)

DR. MATOBA: I think it may, but I don't think we've got --

DR. WEISS: Well, let's just vote this and

discuss it.

DR. BULLIMORE: Is this a straight yes or no?

DR. WEISS: Just a straight yes or no. Just sort of a bottom line. You're a maybe. We can do a maybe if you want to, but let's just do the yeses right now.

(Show of hands.)

DR. WEISS: So we have three yeses. Okay. Four yeses, and consumer and industry can voice their opinion as far as this goes.

How many would vote maybe?

(Show of hands.)

DR. WEISS: Okay. We've got six maybes.

MS. THORNTON: Five.

DR. WEISS: We have five maybes, and how many feel that it has no benefit? How many are nos?

(Show of hands.)

DR. WEISS: One no, and we've got a total here of 10. Okay. So that might indicate why there might be some discussion on this one. So basically, four of us at this point in the discussion feel that there is definitely a significant improvement and five are not sure and one does not think there's a significant improvement and clinical or functional, clinical or functional as opposed to anything else. So then, the next question would be then how to scribe that opinion.

Dr. Grimmett?

DR. GRIMMETT: Michael Grimmett.

Just reiterating a point Dr. Matoba made earlier, in the absence of seeing the comparison data, for example, on the symptom charts between CustomCornea and conventional patients, I'm really unable to answer the question regarding is there any clinical or functional? Certainly from a patient's perspective, I would want to know that. That's why I can't say for certain with the question clinically or functionally is it better, notwithstanding the data that we've seen regarding contrast sensitivity and these other measures that we see some improvement over conventional LASIK. I don't know if it makes a clinical difference. I don't believe I've seen the data that convinces me of that.

DR. WEISS: Dr. Bradley, and then Dr. Maguire.

DR. BRADLEY: Just a general comment that as optical quality gets better, at that point, one can only improve things by small increments. At that point, the opportunity for dramatic visual improvement is basically eliminated. So posing the question using traditional clinically significant or functionally significant terms may not be appropriate when we get into wavefront correction because we are dealing with very subtle effects and we're looking for small improvements that may only be

observable when you look at population means, but for each individual patient and what's the clinical significance of, let's say, half a line improvement in acuity, I think we'd all argue probably very little, but if that's what the procedure does, then it is a significant improvement. Can you argue that it's clinically or functionally significant? I think that's the point.

DR. WEISS: I think we would probably want to get the opinion of the consumer rep, but I personally would believe that it would be important to convey that to the patient to counter any claims of super-human normal animalistic eagle vision, et cetera.

(Laughter.)

DR. WEISS: So Glenda?

Ms. Such, do you have any opinion from a consumer standpoint, what do you think the consumer would want to know or have conveyed to them when they're trying to decide whether they should have customized treatment?

MS. SUCH: Actually, I've got quite a lot to say, only because I'm sitting here and have a version of it up right now and am reading through, and because this is the next, well, seventh generation of this particular thing, that a person who's coming in new to this, not having been in Version 1 through 6, that the patient who's getting this is going to, by the wording in the pamphlet

I'm seeing so far, is going to feel as though this is the new, the improved, and is resolving all the issues that were causing the symptoms or causing the bad effects before.

There's a lot of wordage in the particular pamphlet that we have that's talking about, you know, what exactly is causing the problem with the vision and all this stuff. When I first started reading this, I thought, wow, the sponsor really deserves a lot of credit for this because it's really educating people, and then there's like this quantum jump to because of the eye movement and there's eye movements in every single person that they did, there was 100 percent of the people had eye movements, and then there was another jump, you know, to say that this would resolve this and this would then be able to make sure this didn't happen anymore, and that type of wording, although accurate, is going to lead people to think that, oh, well, you know, I know people that had this surgery. They had some problems, but it was probably because of that, and you are faced with people who are thinking that this is going to give them the ability to not have to wear glasses again or any form of glasses, and I'm seeing people that that's not true on just in my work experience, seeing people, and they have been given the impression that they are going to get results so they don't have to wear any

eyewear at all, and you know, there's some phrasing in here that because we're all in the field, we're so used to hearing the words that we get caught up and everybody knows what they mean.

I mean, refractive error is such a common phrase among us, that it was like duh, but in the same sense, most people when you say to them, you know, that it's going to make it so perhaps if the surgery has a little problem, that you might have a slight increase in your refractive error and you may have to have a little difference in your glasses, they don't really know what that means. They don't mean that the reason that they got this surgery in the first place was because they felt that glasses were too thick and now they're going to have even thicker glasses.

There's phrasing like that that's within here that's a little bit concerning to me. The time that's spent in going over, you know, that the eye is like a camera with a film, I always liked that for most consumers because most consumers are not as high end as we are in knowing about things and need analogies, but you know, it suddenly does this jump again. It does a jump into the scientific. If you're going to start that way, finish that way, and I think that, you know, you need to be honest about that this is a cosmetic surgery that is going to

allow you to perhaps not have to wear glasses, and if you do have to wear glasses, that they may be less, you know. They may not have to be as strong, and I think some of the wordings, I was deeply moved by some of the people that talked about, you know, issues around dry eyes, that there's phrasing all through here that's not thorough.

DR. WEISS: Actually, some of that, we will get to when we talk about additional labeling.

MS. SUCH: Okay.

DR. WEISS: What I'd like to do right now is confine this to the first question, which is specifically, whether the differences in the outcomes in this particular laser are clinically or functionally significant. So from a patient standpoint, do you think any of the data that you've been shown today demonstrates to you that there are certain things that are clinically or functionally significant, and if so, which are these and what do you think a patient would want to know about?

MS. SUCH: I don't think -- clinically, yes. I think that a patient should know that if we get some more data that actually supports what has been proposed today, that it works better clinically, that they would want to know that this would enable the surgeon to be able to do this more effectively.

I think functionally, it's not saying a lot of

difference. It's saying that there's some difference, but I don't necessarily see that it's produced a significant difference functionally.

DR. WEISS: Okay. Thank you.

Dr. Maguire?

DR. MAGUIRE: One obvious important clinical outcome is the level of uncorrected visual acuity after the first event, and as Dr. Huang has said and I concur and I think most of the other people here concur, there's insufficient numbers in the higher levels of myopia that are being requested for approval to say that this is as accurate and has just as minimal scatter as for lower levels, and the reason that's important are a few.

Number 1.

DR. WEISS: Actually, I think that's going to go to Question, perhaps, Number 2. I still want to confine ourselves to the benefit of this over conventional. We're going to get to -- we can discuss in a little bit whether the range --

DR. MAGUIRE: Right. I agree and I understand what you're saying, but describing the higher-order aberration correction, it's kind of building a church. You have the basic lower-order aberrations are the basic portion of the building, and then the higher-order aberrations, that's the steeple on the top, and if you have

a bad foundation, then higher-order aberration correction doesn't really make a whole lot of difference functionally.

DR. WEISS: Then what I'd like to do is, I think you're speaking about above -5?

DR. MAGUIRE: Yes.

DR. WEISS: What I'd like to do, Leo, is at a little bit later down the line, discuss the above -5 but get back, let's say, to the -- we can even discuss less than -5 and that category where we're satisfied with the postop uncorrected and best-corrected visual results.

Do you feel that there is an advantage, clinical or functional, of customized over traditional?

DR. MAGUIRE: If the data shows that now. What it looks like is there's a much higher level of subjective packings in the lower levels of correction.

DR. WEISS: We're going to have Dr. Owsley speak, then Dr. Bradley, then Dr. Burns, then Dr. Bullimore, then Dr. Bandeen-Roche.

Okay. Dr. Owsley?

DR. OWSLEY: I just want to go back to, I guess, emphasize my own perspective that we can't really answer this question from the patient's point of view because one of my colleagues on the panel has already mentioned, we don't have the relevant patient report data to answer that question.

The other way you get patient-centered functional information is by looking at visual performance measures, and we don't have those either in this study. So from the patient's perspective, I don't think we can answer that question because the data aren't available.

DR. WEISS: What I would suggest is what could be put in the patient insert, if the panel wanted, is something to the effect that there's no evidence of a higher satisfaction rate in patients with customized treatment versus conventional treatment.

Mr. Whipple?

MR. WHIPPLE: Yes. Jayne, very quickly, just as guidance, when we're talking about labeling claims in that patient booklet.

DR. WEISS: Yes.

MR. WHIPPLE: Much of that will also spill over into advertising and promotion as well. So just kind of keep that in mind when you're talking about how you might craft words or something like that.

DR. WEISS: The other thing, and I'll defer to you, is if the data is available at a later point from the sponsor, we could pen something like that until such time as the sponsor gives us the data showing that there is a higher satisfaction or that there was better visual performance in those that they treated conventionally,

excuse me, those they treated with customized treatment and then I assume the patient insert could be changed appropriately to reflect that.

MR. WHIPPLE: Yes, and that is an option for this panel.

DR. WEISS: So that, it doesn't have to be available this exact moment, but unfortunately the panel has only to go by the data that we have here presently.

Dr. Bradley?

DR. BRADLEY: Yes, I was really going to repose the question to Dr. Owsley, and it seemed to me there are two types of data that could be applied to this question, one being the performance data that we have, low contrast acuity, high contrast acuity, contrast sensitivity, photopic and mesopic, and we have that comparison data between the Custom LASIK and the conventional LASIK.

What we do not have is the subjective reports in a comparison between Custom and traditional and that's what I think people are asking for. So I'm going to bring us back to the data that we do have which is the performance data.

DR. OWSLEY: Can I just clarify? I'm using the word "performance" in a different way. What the sponsor has done is measure visual function. Okay. Visual performance data would be data from the performance of

visual IADLs, like a big one that comes before panel all the time, I know, is driving.

DR. BRADLEY: Yes.

DR. OWSLEY: So we don't have that kind of data, and it's often those types of instrumental activity of daily living problems that patients are talking about when they say they have visual problems. They're not talking about how they performed on the grating test or the letter acuity chart. So I just want to clarify my remarks that it's that kind of functional data we don't have and we most certainly have the psychophysical data.

DR. BRADLEY: So that's what I was going to ask your opinion on because we have those data. The sponsor has shown that with the Custom procedure, contrast sensitivities are higher relative to conventional. The various acuity measures tended to be slightly better with Custom versus conventional.

Now, if presumably it would be possible to ascertain whether those differences were statistically different, significantly different, if that were the case, would it be reasonable for the sponsor to put in labeling that improvement in vision is likely? How would it be possible to accurately and meaningfully communicate these data to the patient in the patient information?

DR. OWSLEY: Well, I can speak to the issue of

driving. The contrast sensitivity differences you see with the conventional technique and the Custom technique are contrast sensitivity levels that are not in the level of contrast sensitivity impairment that would impair driving performance. So I don't think you're in the danger zone. So it'd be more an issue of whether just sort of personal preference, but there's no data that suggests that contrast sensitivity levels in either of these two groups would put somebody at risk, say, for crash involvement or avoiding obstacles on the road, and I suspect the same thing could be said about reading, that we're talking about contrast sensitivity levels that are so high, that you're not going to get a big hit to reading and reading and driving are really the two IADLs that people mention most of the time when you ask them about visual IADLs.

DR. WEISS: Dr. Huang?

DR. HUANG: I just want to be a little bit different from my fellow members, but I just feel that in that issue on the table is really the technology and also that in the current safety and quality of the vision, I don't feel that, you know, it's FDA or sponsor's responsibility to say this is indeed revolutionary or this is super-vision, you know, this is a new creation of the laser surgery.

I think our responsibility should be based on

the data to review to see if the claim is appropriate and to see if it's safe for the lay public. So I would like to, you know, focus our discussion based on the data rather than asking for more, especially in the subjective data, you know. I feel that, you know, intrinsically, that LASIK patients, there are millions of patients already have a LASIK surgery. So that LASIK surgery is somewhat known already, and I do not feel that it's our responsibility or our obligation to go back to check on if the new technology -- basically what we are reviewing is just Custom software, if it's improving. We are not improving our microkeratome. We are not improving our surgeons' technique. We are not improving on any of the other parameters.

So I feel that, you know, subjective symptoms itself, you know, if we need, we can use the reference population. We don't really need to go back to another, you know, study because otherwise we have to go back to ask for data for visual performance. We have to ask for then is the visual performance of the patient after the surgery, are they really better than the patient without surgery or the myopic patients more or less likely to have a visual performance, you know, than the hyperopic patient, and I think we are opening up a Pandora's box, you know, of the questions that we probably would never be able to answer.

The key question here is that if this

technology can reduce the higher-order aberrations, obviously the answer is not there yet, but on the other hand, is it safe or is the quality of vision better? In my opinion, the answer is yes.

DR. WEISS: Dr. Burns?

DR. BURNS: Yes, I just wanted to comment on why I'm firmly in the maybe category, also, is that, we need to keep in mind that the level of aberration differences we're seeing are things that will develop over the next 10 years. In other words, your aberrations increase with age, and so a lot of these variations we just can't know the answer right now to what the long-term differences are. So I don't feel confident saying yes, but I sure don't want to say no.

DR. WEISS: I guess that's a maybe.

Dr. Bullimore?

DR. BULLIMORE: Well, as someone who's maybe in the firmly camp, it's interesting that Dr. Grimmett and I voted on opposite sides, but we were actually in violent agreement on this one. I think we would both agree that the aberrations are improved or less destroyed or whatever word you want to use. We're questioning whether there's visual benefit as assessed with the contrast test, and I'm firmly with him on the issue that there's been no demonstration that whether you think about it in terms of

satisfaction, whether you think about it in terms of symptoms or activities of daily living, as Dr. Owsley likes to refer to them, there's any benefit been demonstrated by the sponsor.

I think we could probably pretty quickly reach consensus on that and work on crafting some verbiage that would capture those sentiments for the agency.

DR. WEISS: That sounds good.

Then we're going to have one last comment on this question and then maybe we can start some crafting.

Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: I keep thinking about validation, and this goes to Dr. Bullimore's comment about the high-tech images that might appear in the literature or Dr. Bradley's point about the first innovation. That is, the objective measurement of vision. Are there validation measures, validation data to support that such objectively measured vision actually does appear better to the patient or whether the simulated charts correspond in any reasonable way to what the patient might see?

DR. WEISS: In relationship to Dr. Bullimore's comment about symptoms and satisfaction and the absence of data, the same sort of statement could be used in the patient insert which is that there's no evidence that the postop symptoms are decreased or that there's a higher

satisfaction rate, but I'll leave it to the panel to start the crafting, if they would prefer another approach.

So Dr. Bullimore, did you want to start? I guess not from that look.

DR. BULLIMORE: I mean, let me give you a couple of little sound bites.

DR. WEISS: That means five seconds or less.

DR. BULLIMORE: Optically, you know, demonstratable optical benefits. Subtle visual differences.

DR. WEISS: Okay. Sound bites without verbs. Okay. So we'll add verbs.

DR. BULLIMORE: Okay.

(Laughter.)

DR. WEISS: Both Dr. Grimmett and I do verbs. Can you repeat the first one?

DR. BULLIMORE: Do you do them together or independently?

DR. WEISS: Separate verbs.

DR. BULLIMORE: Separate verbs.

And the thing I think we can all agree on is no benefit in terms of patient satisfaction, functional performance, or --

DR. WEISS: I don't know if you could say functional performance. Well, can you say it, because the

contrast -- I think we should include the --

DR. BULLIMORE: Well, I mean, I'm using functional in the Dr. Owsley sense of the word rather than the contrast sensitivity sense of the word, and this is where I think it's so important to get the verbs and the nouns and the adjectives right.

DR. WEISS: So, you did the adjectives or the nouns. Maybe we want someone to do the verbs separately.

DR. BULLIMORE: Dr. Owsley.

DR. OWSLEY: Are you trying to write this so the patient understands it?

DR. WEISS: Well, first, we're going to try to come up with a sentence and then we'll go on from there.

DR. BULLIMORE: I'd like to buy a vowel.

DR. WEISS: We don't have anyone spinning the wheel today, though.

DR. BULLIMORE: Thank you, Vanna.

DR. OWSLEY: When we use visual performance and those sorts of phrases with patients, those are sort of scientific.

DR. WEISS: I think Dr. Grimmett is actually going to add nouns and verbs and adjectives together.

DR. GRIMMETT: Mike Grimmett.

I think we have two concepts on the table, and I believe we have actually consensus on them, as Dr.

Bullimore suggested. Number 1, as Dr. Owsley stated, there's no data to support higher functional performance, and I put parenthesis, activities of daily living, such as reading or driving, end parenthesis, or satisfaction rates in patients with customized treatment. That's Issue Number 1.

Issue Number 2.

DR. WEISS: I think you'd have to say customized versus conventional treatment.

DR. GRIMMETT: Sure. Issue Number 2, Dr. Bradley stated, is that while data can be provided, the psychophysical data can be provided that is slightly better, such as low and high contrast visual acuity, low and high contrast sensitivity measurements, the relation to satisfaction or IADLs is actually unknown.

There's a theoretical benefit by all those visual functional performance measures that were obtained. There is a theoretical benefit. We all agree that we'd like to see those better. We just don't know for everybody.

DR. WEISS: Dr. Bradley, and then Dr. Maguire.

DR. BRADLEY: As a failed English language student in England, I'm always nervous at making concise statements, but does this work? Wavefront-guided LASIK has demonstrated slightly superior optical performance than

conventional LASIK and minor improvements in visual acuity and contrast sensitivity.

DR. WEISS: When you say optical performance, what do you mean? What is optical performance?

DR. BRADLEY: Reduced monochromatic aberrations.

DR. WEISS: I would personally prefer to say that because optical performance again makes me think I might see like an eagle.

DR. BRADLEY: Well, the reason I didn't say reduced monochromatic aberrations is because as we saw this morning, even we needed a lecture on what they were, and I think the patient would have no idea what they are. So I was trying to think of a wording that would keep the flavor of it for the patients and slightly superior optical quality, I think, would be consistent with that data and minor improvements in visual acuity and contrast sensitivity would also be consistent with that data.

DR. WEISS: Perhaps we could state that sentence. If you could restate the sentence and then we could have a little discussion on the sentence or if there's consensus on the sentence?

DR. BRADLEY: Wavefront-guided LASIK has demonstrated slightly superior optical quality than conventional LASIK and minor improvements in visual acuity

and contrast sensitivity relative to conventional LASIK.

DR. WEISS: Any discussion? Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: This may really be better for the next section, but in terms of the data that support the difference, I do have some concerns about that cohort of 50 people, and I would feel much more comfortable if the differences that have been shown were demonstrated in data that were designed a bit more carefully. In other words, concurrent randomization and blinding.

DR. WEISS: Actually, I think we're going to move on to the second question fairly shortly. So we will put that in the second question, but I personally have concerns on the use of that statement because I think it's broad enough as to be, I can see that in one of the throwaways very soon as to imply things that you don't mean by it.

Dr. Maguire?

DR. MAGUIRE: And that's why I think maybe a little something should be added on to the end that says is rarely improved uncorrected vision to 20/10.

DR. WEISS: Dr. Owsley? Dr. Swanson?

DR. SWANSON: In terms of the sentence, we need to remember that 20 percent of people got worse in their low contrast sensitivity. So to where the sentence is, it sounds like you're going to be better afterwards, and we

don't want the sentence to actually say that.

DR. WEISS: So you have concerns on the sentence. Dr. Maguire has concerns.

DR. SWANSON: Yes. I like the sentence overall. I'm trying to refine it. I'm not objecting to it.

DR. WEISS: Dr. Bullimore?

DR. PETTIT: I think relative to conventional LASIK needs to be in there. That's all we're talking about and just as an aside, I was being a little flip earlier, I would value Dr. Owsley's input on how best to capture the activities of daily living sentence that she was advocating there.

DR. OWSLEY: This is Cynthia Owsley.

I thought giving examples of reading and driving -- oh, that's what they're talking about. Okay. Can I make a comment?

DR. WEISS: Yes, Dr. Owsley.

DR. OWSLEY: I don't want to change the subject. I just want to make sure that this is discussed at one point. You asked a question as the chairperson, what would you want to know if you were a patient and you had to answer this question or question similar to this, and the question that I think people like me talking as a consumer and other people like I deal with who have myopia

is am I going to be that rare case that has the problem, and where in any of the patient information -- I'm unfamiliar with the terminology. Is that in the labeling?

DR. WEISS: We can put that in the labeling.

DR. OWSLEY: Because some patients are going to be in the 20 percent who lose one or more line of low contrast acuity. Some patients will not -- you know, maybe the higher myopes are not going to get the big benefit from the reduced refractive error, and that, when you look through the patient information packet, another issue is the dry eye. I have dry eyes going in. A lot of women my age are interested in this procedure. So where is that information presented? I just bring that up as a general issue now.

DR. WEISS: It's not totally in there, but for example, I was going to suggest that in the large dataset that we have, there's Table 35 that has all the symptoms, whether it's slightly worse or severely worse. Table 10 has the loss of best-corrected visual acuity, and there were 8.6 percent who lost one line, which is significant in my book, not just the people who lost two lines, which was a very small percentage, and Table 13 had the loss, the decreased vision and low contrast.

So depending on what the panel wants to do, some of those tables, all of those tables, different tables

or whatever can be put in that, but I still want to try to finish off this particular question and try to put it to rest so we can go on to the other questions.

Dr. Swanson?

DR. SWANSON: Yes, to finish the point I was making about, first of all, we want to make it clear that that was an average. The other thing is in terms of being super-vision, half of the people who went through this, their uncorrected visual acuity afterwards was not as good as the best spectacle-corrected visual acuity before. That's the number. We have 52 -- it's 47.5, if you want to do it that way. Basically half of the people ended up with uncorrected visual acuity after the operation that was worse than the best spectacle-corrected had been, and if something about that is in the sentence, then they understand we're saying it might offer some improvements over conventional, but it's not saying it's going to being super-vision because, as I said, half of the people didn't get as good as spectacles could have done.

DR. WEISS: Mr. McCarley?

MR. McCARLEY: Yes, I'll try to represent all the laser industry maybe with one point here.

I hope that with the stroke of a pen, you don't obsolete all current products that don't have LADARVision, the new version, that corrects aberrations. So I would

just, Number 1, if there is a comparison being drawn, I think it should be drawn against the control that they were using, which is the conventional LADARVision, I think that's what it was, rather than all conventional standard LASIK. That's what I'm trying to say.

I'm not sure you can make a broad statement that says if you have this, and again it's the medical-legal issues, what happens when a doctor treats his patients with the current technology, not the upgraded aberration instrument, and the patient's outcome doesn't come out like they want to? Automatically, are they going to be sued because they're not using the state of the art? I'm just concerned about issues here that with the stroke of a pen, you just wipe everyone in the market out. I think it's a great technology.

The only question I would ask is if you had to have LASIK today, would you pick something as advanced as this that may offer potential benefits or what you already know is the standard? You know, for myself, I think I would, if it costs the same, if obviously the safety and efficacy is the same, why would you choose something less?

DR. WEISS: Well, I think it's an important point you raise, that in that sentence, we can easily put conventional treatment with this laser versus customized treatment with this laser. So that's a good point.

Dr. Grimmett?

DR. GRIMMETT: No comment.

DR. WEISS: I would appreciate perhaps if you read the few options that we had for this particular issue and then maybe we can come up with some final statement. We have, I think, Dr. Bullimore's version, Dr. Bradley's version. Was there a Dr. Bullimore version?

DR. GRIMMETT: Mike Grimmett.

I didn't get Dr. Bullimore's version down on paper. Dr. Bradley stated that wavefront-guided LASIK has demonstrated slightly superior optical quality (reduced monochromatic aberrations) compared with conventional LADARVision LASIK and minor improvements in visual acuity and contrast sensitivity relative to conventional LADARVision LASIK.

We could actually just add a comma there and put Dr. Owsley's statement, then put but there is no data to support higher functional performance (activities of daily living, such as reading or driving) or satisfaction rates in patients with wavefront-guided LASIK.

DR. OWSLEY: Instead of higher, how about better? Instead of higher, use the word "better."

DR. GRIMMETT: Better? Okay.

DR. WEISS: I have to say I don't know if anyone else is concerned with the term, and if I'm the only

one concerned, we'll move on, of what was the initial optical? What's the first phrase?

DR. GRIMMETT: Where I added --

DR. WEISS: Yes, because it's incorrect and that's not going to make it.

DR. GRIMMETT: Slightly superior optical quality.

DR. WEISS: Okay.

DR. GRIMMETT: One option was to modify that, what you meant by that.

DR. WEISS: I'm just concerned the quote's going to be that we're all going to read that you have better optical quality with this laser and that's not what the intent of the statement is and that I have a concern about that.

DR. BULLIMORE: This is Dr. Bullimore.

That's what I think the data, the only thing that the data show convincingly is the superior optical quality.

DR. MATOBA: This is Alice Matoba.

I agree, and actually I would have taken the word "slightly" out of there. I think it's more than slightly improvement in optical quality.

DR. WEISS: Okay. So no one else has the same concern about that word? Okay. That's fine.

DR. BANDEEN-ROCHE: Well, I do a little bit. As a non-ophthalmologist, you know, I would interpret optical quality to mean that I'm going to see better.

DR. MATOBA: Compared to conventional?

DR. BANDEEN-ROCHE: Compared to conventional and so what we saw was slight differences in average contrast sensitivity and certain measures of visual acuity, plus the aberration measures which I think we've said we don't know how that affects optical quality as I can perceive it.

DR. MATOBA: But the optical quality refers to the aberration measurements.

DR. WEISS: I think by putting it in parentheses, it will be easily open to misinterpretation. I'm going to defer to Glenda on this.

From a consumer standpoint, do you think it will be clearly understood by a consumer that if we say optical quality --

DR. GRIMMETT: Reduced monochromatic aberrations.

DR. WEISS: -- is improved, what do you think they'll take away from it?

MS. SUCH: Blank look. No. Could you read the sentence again? I stepped out for just one second, but read the sentence again.

DR. GRIMMETT: I'll just read the first section.

MS. SUCH: Yes.

DR. GRIMMETT: Wavefront-guided LASIK has demonstrated slightly superior optical quality (reduced monochromatic aberrations) compared with conventional LADARVision LASIK.

MS. SUCH: They're not going to get it. Optical, most people, I would say, who are not in this field, when they see the word "optical," I think -- can we just say vision, you know? Can we have --

DR. WEISS: But it's not vision is the problem.

MS. SUCH: Yes, okay.

DR. WEISS: That is the problem.

MS. SUCH: So we're getting sort of stuck.

DR. MATOBA: Wait. Can we hear the whole thing?

DR. GRIMMETT: Yes. The last part I think qualifies it all, when I added in Dr. Owsley's intent, I believe, by saying at the end of it, but there's no data to support improved functional performance and then put in the part about activities of daily living, such as reading or driving or satisfaction rates in patients.

Dr. Matoba's pointing out that Dr. Bradley earlier had talked about that data can be provided

regarding the high and low contrast sensitivity in the frame of contrast and vision. We can add that data separately.

DR. MATOBA: It seems to me that there's significant improvement in the optical aberrations, the higher-order aberrations. It's just the contrast and the patient satisfaction we're not sure about. You could clearly mention all of that and separate that out. I don't see why that all could not go into the labeling.

DR. WEISS: You know, I'm going to defer to Mr. Whipple at this point just in the interest of time. I think you're getting the sentiment of the panel.

MR. WHIPPLE: Exactly.

DR. WEISS: Which is that we don't know if patients are any happier. We don't know if their symptoms are any less. We do know the contrast data looks somewhat better. We don't know what it means. We do know the aberration stuff looks better. We don't know what it means. Is there a way for someone at the FDA to pen that in a clearer fashion in the label to perhaps come up with the --

MR. WHIPPLE: Right. I think we can take this as guidance and develop it.

DR. WEISS: Okay.

MR. WHIPPLE: But I'd also like to remind you,

though, as you struggle with the patient labeling, we also need some recommendations for the physician part of the labeling as well.

DR. WEISS: Maybe we'll have one or two more comments on this question and move on, and Dr. Bradley?

DR. BRADLEY: Yes, it's interesting we have struggled now for about half an hour with this question, and in reality, for the patient, we have already heard today from the sponsor and I presented some data, too, that the magnitude of all of the aberrations amounts to maybe .2, .25 diopters equivalent, and these patients are having 4 or 5, whatever, diopters of myopia corrected, and the accuracy of the correction of the myopia, the spherical equivalent myopia, if that was off by .2 diopters, that would bury any advantage produced by correcting the monochromatic aberrations. So that big effect is still the correction of myopia. That's the big effect on vision. That's going to be the biggest impact for the patient, and if we're making statements here, although it's important for us to make statements about the monochromatic aberrations in terms of the patient information, it's very important that they understand that this is not the big effect here. The big effect is the correction of their myopia.

DR. WEISS: Then maybe you can actually add

that as a statement. The major beneficial effect of this laser is the treatment of myopia and you could actually put that as a phrase because I agree. I mean, the difficulty I think the panel is having is to convey a very, very -- the new technology which has a minimal import versus the old technology which has a maximal import.

DR. BRADLEY: That's correct, and I think, also, and I had it in my presentation, the statement should be very clear that this technique does not reduce aberrations or improve optical quality relative to preop best-corrected conditions.

DR. WEISS: Okay. That's an important statement as well. So I appreciate that, Dr. Bradley.

So we're going to move on, believe it or not, to Question Number 2. Okay. "Are additional data, analyses or criteria needed to evaluate the relative effectiveness of Custom and conventional treatment with regard to higher-order aberrations and visual function?"

I think Dr. Bandeen-Roche, you were addressing this, and in the interest of time, what I would ask the panel members to do is tell us what you want, tell us what you want, maybe we can get it for you, maybe we can't, but just tell us what you want.

DR. BANDEEN-ROCHE: This is Dr. Bandeen-Roche.

Very briefly, while I think that the data are

very interesting in terms of aberrations, I wouldn't bet my life on that difference standing up because it seems to me that it's reasonable that there could be sources of bias with respect to that cohort, including that they were early on in the study, maybe surgeons got better as the study went along. I don't know if that's reasonable or not. So ideally, I would like to see some data that was concurrent and randomized and assessed in a blinded fashion. You may tell me that's, you know, patently unrealistic. It's not going to happen. Perhaps you could do some matched analyses, you know, where you actually do some analyses that match by approximately the same time in the course of the study, same position, same pupil size, whatever, temperature, that sort of thing that's important.

I guess the second thing that I would like you to do is to assess the variability between sites. Certainly if there is substantial variability, that's important in its own right, but it also means that the assessments of variability of the statistics, things like P values and confidence intervals, aren't valid and that that variability would need to be accounted for in that case, and then finally, I think several of the reviewers in their written reports brought up that there was a real focus on average findings, and I think it would be more important to provide distributions.

So for instance, for stability, I believe Dr. Bradley brought this up, it's not just mean change that matters but the percentage that have some various levels of change, you know, some more focus on reporting distributions and not just means in the statistics.

DR. WEISS: Dr. Burns?

DR. BURNS: As we talk about statistical analysis in future studies, we're going to face the fact that it would be nice to have a well-designed fellow-eye study for things like contrast sensitivity but that won't be useful for things like questionnaires about quality of life or things like that because you don't really know how the two eyes interact. So there will have to be some sort of case-control type of design for that part of the study. So it's going to be a complicated issue to document.

DR. WEISS: I'll go to you, Karen, and then we'll go to you, Leo.

DR. BANDEEN-ROCHE: Just a brief clarification. I didn't even mean randomizing one eye to one treatment and one eye to the other but randomizing patients within the same clinic.

DR. WEISS: Dr. Maguire?

DR. MAGUIRE: I'd just like to say that I think we should require the sponsor to have more people at the higher end of myopia in the level that they're asking for

in the -5 to -7 group. That is something that's been said by at least four, maybe five, people on panel since either written or spoken during this thing, and the rationale for that, Number 1, the N is low. Number 2, as Dr. Bradley's pointed out, this is a thing that does two things, it not only corrects higher-order aberrations but it also uses the wavefront analysis to measure myopia, and there's no clear data that it's just as accurate at measuring high myopia as low myopia, and we need the numbers to prove that it's at least equivalent to conventional LADARVision correction because we don't know that because we're comparing a subjective measurement of refraction to the other.

The third reason for doing it is, is because the initial cohort is much bigger and it's reduced because it fell short when it was correcting higher rather than lower degrees of astigmatism, and so it's reasonable to hypothesize that it may fall short measuring higher degrees of myopia and lead to scatter.

DR. WEISS: Well, at this point, I don't think we can get more patients who are above -5 because my assumption is we got all the patients that you had that were above -5. So the only way that I can see, and Mr. Whipple can add anything to this, is that you have a postmarket study, if you want it above those people, or you limit the approval to up to that level. Any other way that

we could do this?

MR. WHIPPLE: Well, I think what you're saying basically is you need these additional analyses if they're going to make more specific claims about the success of their device over what is being allowed, what we're discussing here today. So that may have to come in as a supplement, that may have to come in as additional information to make other specific claims later on. What can you say about the data we have here today?

DR. WEISS: Are you comfortable with the data we have here today, Leo, in terms of saying that the range of approval would go up to -7?

DR. MAGUIRE: No.

DR. WEISS: So you would want to cut it off at -5?

DR. MAGUIRE: If I read Dr. Huang right, he isn't either, and I think I'd be interested to see what other people are not comfortable and for the reasons we discussed.

DR. WEISS: So then, I'll go back, Mr. Whipple. If, let's say, Dr. Maguire, Dr. Huang, were not comfortable in extending the approval to -7, the only two ways that I see to go about it is to have it extended with postmarket surveillance of that higher range of myopes or to limit the indication up to -5, is that correct? Is there any other

way to go about it?

MR. WHIPPLE: Well, I don't think the postmarket issue, I think that's more of an issue where you do have this clinical study in the higher ranges with additional data coming in as a supplement later. You can as an option take the indication and say that the data here only support to a certain range and you can recommend that as you so choose.

DR. WEISS: Okay.

DR. HUANG: My written recommendation, and I did not think the range of indications should be from -1 to -7. I think it should be higher than that and should be -1 to -6 or -1 to -5.

DR. WEISS: Mr. Whipple, and then Mr. Bradley.

MR. WHIPPLE: I was just simply saying that that is something that is an option for you to consider. So you may want to discuss that further here to make sure everybody agrees.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: Dr. Maguire raises an interesting point I had talked about before. There are possible reasons for this technology whereby it would not do a good job of measuring aberrations and indeed myopia in very highly myopic eyes because of the dot quality in the Shack-Hartmann aberrometer, and I wonder if you have a sphere

correction built into your device. I'm talking to the sponsor now.

DR. WEISS: The sponsor could approach the panel just to answer the question at the podium. If you can identify yourself first, please?

DR. PETTIT: Okay. I'm George Pettit with Alcon.

I'm sorry. Dr. Bradley, could you just restate the question one more time?

DR. BRADLEY: The issue is with very high levels of myopia and the highly curved nature of the exiting wavefront here, there's significant curvature over the affected aperture of your lens and therefore the dot quality in your final dot image is degraded and the potential is that you cannot accurately measure the myopic aberrations because some instruments put a variable collar correction for the myopia in because of that very problem.

Does your instrument have that?

DR. PETTIT: We do not have that particular feature. We have some optical features to get the largest dynamic range that we can using a static optical design, and we have validation data demonstrating the accuracy using test reference pictures of different myopic and various astigmatic and comatic power and whatnot, and we've supplied some of that to the agency. We can, if it's

important, we can supply specific information demonstrating the accuracy of myopia up to the requested approval range, but we have very high accuracy and we can demonstrate that data with the measurement.

DR. BRADLEY: Yes, I think if you demonstrated that to the agency, there's no reason, if it works for your model eyes in your calibration, it should also work for this.

DR. PETTIT: That is the case.

DR. WEISS: Dr. Grimmett?

DR. GRIMMETT: Michael Grimmett.

Just a comment. It's known from prior PMAs and experience with all these devices that the predictability and effectiveness falls off at higher ranges. It's also typical that the higher ranges have less patients in the subset. I'm against limiting the approval because there's no red flags that are being raised at this point that there's anything inherently wrong with higher ranges.

I certainly understand the N is too low to make precise determinations, but because this is an algorithm change and we know what conventional LASIK does with a LADARVision unit, unless alarmed about the higher scatter and the higher ranges simply because it's typical of what happens with other devices.

Additionally, given the further information

that was just presented that they have accuracy data from model eye information, assuming that that's valid and been reviewed by the FDA, I'm not in favor of limiting the range of approval.

DR. WEISS: So just to sort of see where we are with this particular question, which has nothing to do with Question 2 by the way, but in any way, 2A perhaps, I'd like to just have a straw poll vote in terms of those who would like to limit the approval to up to -5, if they could raise their hands.

(Show of hands.)

DR. SWANSON: I've got a question before I can answer that.

DR. WEISS: You can't do that. The Chair asked the question, you've got to answer. It's the prerogative of the Chair. You can ask your question afterwards, though.

DR. SWANSON: I don't know what you mean.

DR. WEISS: So you have a yes, no or --

DR. SWANSON: I can't answer.

DR. WEISS: Can't answer. Okay. So we've got three who would like to limit it. Down here. And how many would say they do not want to limit it?

(Show of hands.)

DR. WEISS: I've got four who do not want to

limit it, and then how many are abstaining?

(Show of hands.)

DR. WEISS: We have three abstaining.

Dr. Swanson, ask your question.

DR. SWANSON: In terms of limit of the approval, I don't understand exactly what that means. There's a list of precautions saying that it hasn't been established beyond a certain amount.

DR. WEISS: Well, we would be saying that basically this is FDA-approved. If the proposal is to vote for approval, it would be voting for approval with the stipulation up to -5 is FDA approved and is not FDA approved for anything beyond -5. That's what the question is. The concern has been brought up by some members of the panel.

DR. SWANSON: Right. No, I understand that. I'm just trying to look at how it goes. So in other words, if a physician used it --

DR. WEISS: It's an off-label use.

DR. SWANSON: Then it would be off-label use.

DR. WEISS: Off-label.

DR. SWANSON: Right. Thank you.

DR. WEISS: So we're definitely sort of split on this.

Mr. McCarley?